METHOD OF INHIBITING BODY FAT STORES

CROSS-REFERENCE TO A RELATED APPLICATION

This application is a continuation-in-part of our co-pending application, Ser. No. 837,148, filed Apr. 7, 1986, now U.S. Pat. No. 4,659,715, issued Apr. 21, 1987.

BACKGROUND OF THE INVENTION

This invention relates to a method for reducing body fat stores in vertebrate animals without causing significant weight loss by administering to the animal an agent to suppress its prolactin secretion.

A method for reducing body fat stores without causing significant weight loss would be valuable to the livestock industry as a better grade of meat could be obtained without a concomitant lowering of the price paid per animal due to weight loss. In humans, such a method would be valuable to athletes who strive to obtain a low percentage of body fat without a loss in muscle mass.

It is, therefore, an object of this invention to provide this method.

THE INVENTION

In accordance with the method of this invention, it has been found that inhibiting the pituitary gland's production of prolactin will result in body fat stores being reduced in vertebrate animals without significant body weight loss.

Inhibiting prolactin secretion is effected by administering, to the animal, a pharmaceutically appropriate dose of a prolactin-inhibitor, such as various ergot-related compounds. The dosing may be by oral or by peritoneal, e.g., subcutaneous or intramuscular injection, administration.

Exemplary of ergot-related prolactin-inhibitors are: 2-bromo-α-ergocryptine; 6-methyl-8β-carbobenzyloxy-aminomethyl-10α-ergoline; 1,6-dimethyl-8β-carbobenzyloxy-aminomethyl-10α-ergoline; 8-acylaminoergolenes, such as 6-methyl-8α-(N-acyl)amino-9-ergolene and 6-methyl-8α-(N-phenylacetyl)amino-9-ergolene; ergocornine; 9,10-dihydroergocornine; and D-2-halo-6-alkyl-8-substituted ergolines, e.g., D-2-bromo-6-methy-8-cyanomethylergoline. The foregoing ergot-related compounds and the processes for their formation are known to the art. From the standpoint of side effects, especially that on fertility, 2-bromo-α-ergocryptine has been found to be highly suitable for the method of this invention.

The non-toxic salts of the prolactin-inhibiting ergot-related compounds formed from pharmaceutically acceptable acids are also useful in the method of this invention.

Different animal species exhibit dissimilar prolactin-inhibition sensitivity to ergot-related compounds. Hence, the dosage required to obtain significant reductions in body fat stores varies over a fairly wide range. In fact, it has been found that a proper dosage range for a selected animal species also can be quite wide. For example, a study of golden hamsters showed that an intraperitoneal daily dose, as low as 0.15 mg/kg body weight and as high as 6.00 mg/kg of body weight, of 2-bromo-α-ergocryptine in divided doses of two times a day for a 24-day period gave good reductions in body fat stores without significant losses in body weight. Thus, the suitable dosage range is best determined empirically for each animal species. Generally, the minimum dosage to obtain the body fat stores reduction sought will be the preferred dosage as the chance of unwanted side effects is diminished and the cost of dosing will be kept to a minimum. As a guide, most animal species upon which the method of this invention would be used commercially, e.g., swine, ruminants and humans, will exhibit the body fat store reduction desired with daily intramuscular dosages of 2-bromo-α-ergocryptine within the range of from about 0.15 mg/kg body weight to about 6.0 mg/kg body weight.

Capsules or tablets containing the unit doses of the ergot-related compound are suitable for oral dosing. Generally, the ergot-related compound will be used as a pharmaceutically acceptable salt when administered orally. If peritoneal dosing is used, the ergot-related compound will be provided with conventional sterile diluents, such as, mannitol, sucrose, vegetable oil, etc. The duration of administration may vary from species to species.

The period of time over which the dosage of the prolactin-inhibitor is administered is an important aspect of the method of this invention. However, generally, if the animal is for commercial slaughtering, the period of time for dosage should be at least 7 days in length and up to the fifth day before slaughter. It is believed desirable to cease dosing five days before slaughter to allow the prolactin-inhibitor to be substantially eliminated from the animal's system at the time of slaughter. If the animal is being subjected to long-term treatment, in accordance with the method of this invention, then the dosing is first given at the above levels for that period of time necessary to achieve the desired body fat stores level and is thereafter dosed so as to maintain that level for the extended period. In either case, for the dosing to yield significant results, the dosing should be maintained for at least 7 days and preferably at least about 10 days.

It is theorized, though the method of this invention is not limited thereby, that the administration of a prolactin-inhibitor to an animal reduces or abolishes the lipogenic responses of hepatocytes to insulin and severely depresses the hepatocyte insulin receptor number. Since body fat stores are dependent on the synergistic action between prolactin and insulin to increase hepatic lipogenesis, the abolishment of prolactin secretion stills hepatic lipogenesis.

EXAMPLES

Mature (3–7 months old) male golden hamsters, *Mesocricetus auratus* (body weight: 100–150 g) were caged in pairs, fed ad libitum, maintained at 23° C. and provided 14-h daily photoperiods (light onset: 0800 h). The hamsters were injected (i.p.) daily at 0800 and 1400 with 2-bromo-α-ergocryptine (300 ug/0.1 ml peanut oil) or peanut oil (controls). Food consumption was monitored daily. After 24 days of treatment, the animals were killed by overdose of sodium pentobarbital to obtain body weights, abdominal and epididymal fat pad weights, and testes and seminal vescicle weights. Statistical differences between the two groups were tested by Student's t to determine the significance, "P". The results are given in the table.

In the Examples shown in Table I the 2-bromo-α-ergocryptine treatment reduced ($P<0.01$) abdominal fat weight 47% and epididymal fat weight 32% compared with control treatment. However, 2-bromo-α-